# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

## PCT

### NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

| | |
|---|---|
| **Date of mailing** (day/month/year)<br>03 June 1999 (03.06.99) | |
| **International application No.**<br>PCT/CA98/00792 | **Applicant's or agent's file reference**<br>6580-123 |
| **International filing date** (day/month/year)<br>21 August 1998 (21.08.98) | **Priority date** (day/month/year)<br>22 August 1997 (22.08.97) |
| **Applicant**<br>ETCHES, Robert, J. et al | |

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

19 March 1999 (19.03.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|---|---|
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | Authorized officer<br>S. Mafla |
| Facsimile No.: (41-22) 740.14.35 | Telephone No.: (41-22) 338.83.38 |

# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BERESKIN & PARR
40 King Street West. 40th Floor
TORONTO. ONTARIO M5H 3Y2
CANADA



# PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

| | |
|---|---|
| Applicant's or agent's file reference<br>6580-123 | Date of mailing *(day/month/year)*<br>24. 11. 99 |
| | **IMPORTANT NOTIFICATION** |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/CA98/00792 | 21/08/1998 | 22/08/1997 |

Applicant
UNIVERSITY OF GUELPH et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

| Name and mailing address of the IPEA/ | Authorized officer |
|---|---|
| European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Vullo. C<br><br>Tel.+49 89 2399-8061 |

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | **FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
|---|---|---|
| 6580-123 | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/CA 98/ 00792 | 21/08/1998 | 22/08/1997 |
| Applicant | | |
| UNIVERSITY OF GUELPH et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

# INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/CA 98/ 00792

**Box I Observati ns wh re certain claims were f und unsearchable (Continuation f item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13, 18
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 13 and 18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Claims Nos.: 13 18

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

# INTERNATIONAL SEARCH REPORT

[redacted]tional Application No
PCT/CA 98/00792

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 6 C12N15/62 C12N15/13 C07K16/02 C12N5/10 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 94 20608 A (UNIV CREIGHTON ;HODGSON CLAGUE P (US)) 15 September 1994<br><br>see page 1, line 3-5<br>see page 12, line 29 - page 13, line 8<br>see page 55, line 26 - page 57, line 9<br>see claim 16 | 1,2,7,9,<br>14,15,<br>19,20,22 |
| Y | | 3-6,10,<br>13,16,<br>17,21,<br>23-27 |
| A | | 11,12 |

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-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 10 March 1999 | 23/03/1999 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Covone, M |

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>Y | US 5 080 895 A (TOKORO HIDEO)<br>14 January 1992<br>see the whole document | 18<br>3-6,10,<br>13,16,<br>17,21,<br>23-27 |
| X | WO 97 08307 A (IL DONG PHARMA ;KIM SUN YOUNG (KR); KIM KEE WON (KR); KIM TAE HAN)<br>6 March 1997<br>see page 1, line 9-11<br>see page 2, line 9-25<br>see page 19, line 21 - page 20, line 13 | 1,7 |
| X | ETCHES R J ET AL: "CHIMERIC CHICKENS AND THEIR USE IN MANIPULATION OF THE CHICKEN GENOME"<br>POULTRY SCIENCE,<br>vol. 72, 1993, pages 882-889, XP002069539<br>see the whole document | 1,7 |
| X | CHEN H.Y. ET AL. : "Vectors, promoters, and expression of genes in chick embryos"<br>J.REPROD.FERT.,<br>vol. 41, no. suppl, 1990, pages 173-182, XP002095934<br>see the whole document | 1,7 |
| P,X | WO 97 47739 A (MACARTHUR WILLIAM C ;UNIV MICHIGAN (US); GENEWORKS L L C (US))<br>18 December 1997<br>see page 3, line 15 - page 4, line 19<br>see page 5, line 33 - page 6, line 7<br>see claims 18,25<br>see figure 1 | 1-10,<br>14-17,<br>20-28 |
| P,X | PATENT ABSTRACTS OF JAPAN<br>vol. 098, no. 002, 30 January 1998<br>-& JP 09 275849 A (EISAI CO LTD),<br>28 October 1997<br>see abstract | 1,7,9,<br>14,15 |
| P,X | DE 196 07 367 A (PROGEN BIOTECHNIK GMBH)<br>28 August 1997<br>see page 2, line 20-25<br>see page 2, line 60 - page 3, line 12<br>see page 4, line 18-27 | 14-17 |

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 98/00792

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9420608 A | 15-09-1994 | AU 699706 B | 10-12-1998 |
| | | AU 6407694 A | 26-09-1994 |
| | | CA 2157931 A | 15-09-1994 |
| | | EP 0688358 A | 27-12-1995 |
| | | JP 8507687 T | 20-08-1996 |
| US 5080895 A | 14-01-1992 | AU 600240 B | 09-08-1990 |
| | | AU 6564886 A | 28-05-1987 |
| | | CA 1306946 A | 01-09-1992 |
| | | DE 3689717 D | 21-04-1994 |
| | | DE 3689717 T | 20-10-1994 |
| | | EP 0225254 A | 10-06-1987 |
| | | ES 2052496 T | 16-07-1994 |
| | | MX 171572 B | 08-11-1993 |
| | | JP 2034005 C | 19-03-1996 |
| | | JP 7053669 B | 07-06-1995 |
| | | JP 62215534 A | 22-09-1987 |
| WO 9708307 A | 06-03-1997 | AU 6756396 A | 19-03-1997 |
| | | EP 0851917 A | 08-07-1998 |
| WO 9747739 A | 18-12-1997 | AU 3479997 A | 07-01-1998 |
| DE 19607367 A | 28-08-1997 | NONE | |

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| 6580-123 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/CA98/00792 | 21/08/1998 | 22/08/1997 |
| International Patent Classification (IPC) or national classification and IPC<br>C12N15/62 | | |
| Applicant<br>UNIVERSITY OF GUELPH et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 19/03/1999 | 24. 11. 99 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Schwachtgen. J-L<br>Telephone No. +49 89 2399 8933 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA98/00792

## I. Basis of th report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-29 as originally filed

**Claims, No.:**

1-28 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Yes: | Claims 3-6, 10, 12, 19, 21, 24-28 |
| | No: | Claims 1, 2, 6-9, 11, 13-16, 18, 20, 22 |
| Inventive step (IS) | Yes: | Claims 3-6, 10, 12, 21, 24-28 |
| | No: | Claims 1, 2, 6-9, 11, 13-16, 18-20, 22 |
| Industrial applicability (IA) | Yes: | Claims 1-12, 14-17, 19-28 |
| | No: | Claims |

2. Citations and explanations

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

Re Item V

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following document/s/:

D1: WO 94 20608 A
D2: Parren PW. Hum Antibodies Hybridomas, 1992, vol 3(3), pages 137-145 (abstract)
D3 Hassan JO and Curtis R. Infection and Immunity, 1996, vol 64(3), pages 938-944
D4: US 5 080 895 A

The documents D2 and D3 were not cited in the international search report. Copies of the documents are appended hereto.

1. The present application relates to an expression system for the delivery of proteins to eggs.

   The examples given demonstrate that:

   a) human antibodies injected into hens are transported into the developing chicken egg
   b) recombinant antibodies wherein the constant region is derived from human immunoglobin (Ig) are deposited in the chicken egg
   c) recombinant antibodies are transported to the chicken egg by binding via the CH2-CH3 constant region derived from human immunoglobin to a receptor homologue of the mammalian FcRn

   Items a) to c) represent the contribution made by the invention of the present application over the prior art. Claims 3 to 6, 10, 12, 21 and 24 to 28 of the present application, insofar as these claims can be understood (see Section VIII), seem to address items a) to c). However, the remaining claims concern subject-matter which is known or was obvious from the prior art.

2. Claims 1 and 2 concern an expression system comprising a first DNA sequence encoding a recombinant protein and a second DNA sequence which targets the protein to the egg of an animal. Claims 6, 9, 11, 14, 15, 20, 22 and 23 refer to applications of the expression system of independent claim 1.

Document D1 discloses chicken embryos and transgenic chicken (page 56, lines 1-8 and 31-33) harbouring an expression system comprising a first sequence encoding recombinant bovine growth hormone (BGH) and a second sequence encoding the chicken ovalbumin promoter and a signal sequence (page 56, lines 22-23; claim 16). The signal sequence binds to the developing oocyte, thereby targeting the heterologous protein to the egg (page 56, lines 27-31). The expression system of document D1, thus, anticipates all the technical features of independent claim 1 and dependent claim 2, which do not meet the requirements of Article 33(2) PCT with regard to novelty.

The same objection applies to claims 6, 9, 11, 14, 15, 20, 22 and 23.

3. Expression vectors comprising sequences encoding humanized antibodies are known in the prior art (e.g. Document D2). The vectors comprise rodent Ig variable and human constant sequences and regulatory sequences for the expression of the antibody and are suitable for delivering a recombinant antibody to an egg. The subject-matter of claims 7 and 8 is, thus, not novel and does not meet the requirements of Article 33(2) PCT with regard to novelty

4. Claim 13 concerns a method of preparing an egg that is free of a pathogen by introducing an antibody specific for the pathogen into the egg-laying animal.

Document D3 discloses a method of preparing eggs which are free of Salmonella by introducing antibodies into the egg-laying hens by vaccination with Salmonella. The Salmonella-specific antibodies are transported to the eggs and detected in the egg yolk (page 939, column 2, last paragraph).

The subject-matter of claim 13 is, thus, anticipated by the method described in document D3 and does not meet the requirements of Article 33(2) PCT.

5. Claims 16 and 18 concern an egg containing a recombinant antibody and a method of immunising an animal by administering such eggs.

Document D4 discloses eggs containing a maternal antibody against a specific antigen (column 5, lines 49-56). The egg is fed to an animal to treat or infect infectious diseases (column 8, lines 28-33).

Claims 16 and 18, thus, do not meet the requirements of Article 33(2) PCT with regard to novelty.

6. The subject-matter of claim 19 does not appear to meet the requirements of Article 33(3) PCT. It relates to a transformed avian cell line that secretes a recombinant antibody. However, transformed avian cell lines expressing recombinant proteins, on the one hand, and recombinant antibodies on the other hand, are well known in the art. It therefore appears obvious that the skilled person could combine these features in order to arrive at the subject-matter of claim 19 without exercising inventive skill.

7. For the assessment of the present claims 13 and 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to a method for treatment of the human or animal body.

## Re Item VIII

### Certain observations on the international application

1. The claims of the present application go beyond the invention as supported by the

application (Article 6 PCT) and the description does not enable the skilled person to carry out the invention as claimed (Article 5 PCT).

Claims 1 to 11, 13 to 18 and 20 to 28 refer to eggs in general, while the working examples of the description are restricted to chicken eggs and there is no enabling disclosure for carrying out the invention in any egg without undue burden. The Applicants have not established whether a receptor homologue of the mammalian FcRn is present on eggs other than on chicken eggs

2. Claims 3, 4, 7, 23 and 24 refer to an undefined portion of an immunoglobin that can bind to an egg. The claims are drafted in such a way as to attempt to define the subject-matter in terms of the result to be achieved. In this instance the use of such a formulation renders the claims unclear in scope and is not justified by the disclosed means of achieving the desired result. Moreover, it is possible to define the subject-matter in more concrete terms (i.e. by defining the specific region of the CH2-CH3 region which binds to the avian FCRn receptor). The above claims therefore do not satisfy the requirements of Article 6 PCT.

The same objection applies to claim 2 wherein the DNA sequence which encodes a peptide which can bind to an egg (the solution to the technical problem) is not defined.

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# PATENT COOPERATION TREATY

# PCT

REC'D 29 NOV 1999
WIPO PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| 6580-123 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/CA98/00792 | 21/08/1998 | 22/08/1997 |
| International Patent Classification (IPC) or national classification and IPC<br>C12N15/62 | | |
| Applicant<br>UNIVERSITY OF GUELPH et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 19/03/1999 | 24.11.99 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Schwachtgen, J-L<br>Telephone No. +49 89 2399 8933 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA98/00792

## I. Basis f th report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-29 as originally filed

**Claims, No.:**

1-28 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 3-6, 10, 12, 19, 21, 24-28 |
| | No: | Claims | 1, 2, 6-9, 11, 13-16, 18, 20, 22 |
| Inventive step (IS) | Yes: | Claims | 3-6, 10, 12, 21, 24-28 |
| | No: | Claims | 1, 2, 6-9, 11, 13-16, 18-20, 22 |
| Industrial applicability (IA) | Yes: | Claims | 1-12, 14-17, 19-28 |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following document/s/:

D1: WO 94 20608 A
D2: Parren PW. Hum Antibodies Hybridomas, 1992, vol 3(3), pages 137-145 (abstract)
D3 Hassan JO and Curtis R. Infection and Immunity, 1996, vol 64(3), pages 938-944
D4: US 5 080 895 A

The documents D2 and D3 were not cited in the international search report. Copies of the documents are appended hereto.

1. The present application relates to an expression system for the delivery of proteins to eggs.

   The examples given demonstrate that:

   a) human antibodies injected into hens are transported into the developing chicken egg
   b) recombinant antibodies wherein the constant region is derived from human immunoglobin (Ig) are deposited in the chicken egg
   c) recombinant antibodies are transported to the chicken egg by binding via the CH2-CH3 constant region derived from human immunoglobin to a receptor homologue of the mammalian FcRn

   Items a) to c) represent the contribution made by the invention of the present application over the prior art. Claims 3 to 6, 10, 12, 21 and 24 to 28 of the present application, insofar as these claims can be understood (see Section VIII), seem to address items a) to c). However, the remaining claims concern subject-matter which is known or was obvious from the prior art.

2. Claims 1 and 2 concern an expression system comprising a first DNA sequence encoding a recombinant protein and a second DNA sequence which targets the protein to the egg of an animal. Claims 6, 9, 11, 14, 15, 20, 22 and 23 refer to applications of the expression system of independent claim 1.

   Document D1 discloses chicken embryos and transgenic chicken (page 56, lines 1-8 and 31-33) harbouring an expression system comprising a first sequence encoding recombinant bovine growth hormone (BGH) and a second sequence encoding the chicken ovalbumin promoter and a signal sequence (page 56, lines 22-23; claim 16). The signal sequence binds to the developing oocyte, thereby targeting the heterologous protein to the egg (page 56, lines 27-31). The expression system of document D1, thus, anticipates all the technical features of independent claim 1 and dependent claim 2, which do not meet the requirements of Article 33(2) PCT with regard to novelty.

   The same objection applies to claims 6, 9, 11, 14, 15, 20, 22 and 23.

3. Expression vectors comprising sequences encoding humanized antibodies are known in the prior art (e.g. Document D2). The vectors comprise rodent Ig variable and human constant sequences and regulatory sequences for the expression of the antibody and are suitable for delivering a recombinant antibody to an egg. The subject-matter of claims 7 and 8 is, thus, not novel and does not meet the requirements of Article 33(2) PCT with regard to novelty

4. Claim 13 concerns a method of preparing an egg that is free of a pathogen by introducing an antibody specific for the pathogen into the egg-laying animal.

   Document D3 discloses a method of preparing eggs which are free of Salmonella by introducing antibodies into the egg-laying hens by vaccination with Salmonella. The Salmonella-specific antibodies are transported to the eggs and detected in the egg yolk (page 939, column 2, last paragraph).

The subject-matter of claim 13 is, thus, anticipated by the method described in document D3 and does not meet the requirements of Article 33(2) PCT.

5. Claims 16 and 18 concern an egg containing a recombinant antibody and a method of immunising an animal by administering such eggs.

Document D4 discloses eggs containing a maternal antibody against a specific antigen (column 5, lines 49-56). The egg is fed to an animal to treat or infect infectious diseases (column 8, lines 28-33).

Claims 16 and 18, thus, do not meet the requirements of Article 33(2) PCT with regard to novelty.

6. The subject-matter of claim 19 does not appear to meet the requirements of Article 33(3) PCT. It relates to a transformed avian cell line that secretes a recombinant antibody. However, transformed avian cell lines expressing recombinant proteins, on the one hand, and recombinant antibodies on the other hand, are well known in the art. It therefore appears obvious that the skilled person could combine these features in order to arrive at the subject-matter of claim 19 without exercising inventive skill.

7. For the assessment of the present claims 13 and 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to a method for treatment of the human or animal body.

## Re Item VIII
## Certain observations on the international application

1. The claims of the present application go beyond the invention as supported by the

application (Article 6 PCT) and the description does not enable the skilled person to carry out the invention as claimed (Article 5 PCT).

Claims 1 to 11, 13 to 18 and 20 to 28 refer to eggs in general, while the working examples of the description are restricted to chicken eggs and there is no enabling disclosure for carrying out the invention in any egg without undue burden. The Applicants have not established whether a receptor homologue of the mammalian FcRn is present on eggs other than on chicken eggs

2. Claims 3, 4, 7, 23 and 24 refer to an undefined portion of an immunoglobin that can bind to an egg. The claims are drafted in such a way as to attempt to define the subject-matter in terms of the result to be achieved. In this instance the use of such a formulation renders the claims unclear in scope and is not justified by the disclosed means of achieving the desired result. Moreover, it is possible to define the subject-matter in more concrete terms (i.e. by defining the specific region of the CH2-CH3 region which binds to the avian FCRn receptor). The above claims therefore do not satisfy the requirements of Article 6 PCT.

The same objection applies to claim 2 wherein the DNA sequence which encodes a peptide which can bind to an egg (the solution to the technical problem) is not defined.

We Claim:

1. An expression system for delivering a recombinant protein to an egg comprising (i) a first DNA sequence encoding the recombinant protein and (ii) a second DNA sequence which can facilitate the delivery of the protein to an egg of an animal.

2. An expression system according to claim 1 wherein the second DNA sequence encodes a protein or peptide which can bind to an egg.

3. An expression system according to claim 2 wherein the second DNA sequence encodes a portion of an immunoglobulin protein that can bind to the egg.

4. An expression system according to claim 3 wherein the portion of the immunoglobulin is from the CH2-CH3 region of the Fc domain of the immunoglobulin.

5. An expression system according to claim 3 wherein the portion of the immunoglobulin binds to the Fc receptor on the egg.

6. An expression system according to claim 5 wherein the Fc receptor is the avian Fc receptor neonate.

7. An expression system for delivering a recombinant antibody to an egg comprising (i) a first DNA sequence encoding an immunoglobulin constant region (ii) a second DNA sequence encoding an immunoglobulin variable region and (iii) a regulatory region sufficient to provide for expression of the antibody.

8. An expression system according to claim 7 wherein the constant region is derived from a human immunoglobulin gene.

9. A method of preparing a recombinant protein in an egg comprising:

a) introducing an expression system according to any one of claims 1 to 6 into an egg-laying animal;

b) obtaining an egg containing the recombinant protein; and optionally

c) isolating the recombinant protein from the egg.

10. A method of preparing a recombinant antibody in an egg comprising:

a) introducing an expression system according to claim 7 or 8 into an egg-laying animal;

b) obtaining an egg containing the recombinant antibody; and optionally

c) isolating the recombinant protein from the egg.

11. A method of preparing a recombinant protein in an egg comprising:

a) introducing a transformed avian cell line that secretes a recombinant protein into an egg-laying animal wherein the avian cell line has been transformed with an expression system according to any one of claims 1 to 6;

b) obtaining an egg containing the recombinant protein; and optionally

c) isolating the recombinant protein from the egg.

12. A method of preparing a recombinant antibody in a fowl egg comprising:

a) introducing a transformed avian cell line that secretes a recombinant antibody into an egg-laying fowl wherein the avian cell line has been transformed with an expression system according to claim 7 or 8;

b) obtaining an egg containing the recombinant antibody; and optionally

c) isolating the recombinant antibody from the egg.

13. A method of preparing an egg that is free of a pathogen comprising:

(a) introducing an antibody specific for the pathogen into an egg-laying animal; and

(b) allowing the animal to lay an egg wherein the egg is substantially free of the pathogen.

14. An egg containing a recombinant protein.

15. An egg containing a recombinant protein produced according to the method of claim 9.

16. An egg containing a recombinant antibody.

17. An egg containing a recombinant antibody produced according to the method of claim 10.

18. A method of immunizing an animal comprising administering a therapeutically effective amount of an egg according to claim 16 or 17.

19. A transformed avian cell line that secretes a recombinant antibody.

20. A transgenic egg-laying animal whose germ line cells and somatic cells contain an expression system comprising (i) a first DNA sequence encoding a recombinant protein operably linked to (ii) a second

DNA sequence that facilitates the delivery of the recombinant protein to the egg.

21. A transgenic egg-laying animal whose germ line cells and somatic cells contain an expression system comprising (i) a first DNA sequence encoding an immunoglobulin constant region and (ii) a second DNA sequence encoding an immunoglobulin variable region.

22. A method of producing a recombinant protein in an egg of an egg-laying animal comprising:

(a) preparing a transgenic egg-laying animal whose somatic and germ line cells contain an expression system comprising (i) a first DNA sequence encoding a recombinant protein operably linked to (ii) a second DNA sequence that facilitates the delivery of the recombinant protein to the egg;

(b) obtaining an egg from the animal; and

(c) optionally, isolating the recombinant protein from the egg.

23. A method according to claim 22 wherein the second DNA encodes a portion of an immunoglobulin that can bind to the egg.

24. A method according to claim 23 wherein the portion of the immunoglobulin is from the CH2-CH3 region of the constant region domain of the immunoglobulin.

25. A method according to claim 23 wherein the portion of the immunoglobulin binds to the Fc receptor on the egg.

26. A method according to claim 23 wherein the Fc receptor is the avian Fc receptor neonate.

27. A method for preparing a recombinant antibody in an egg of an egg-laying animal comprising:

(a) preparing a transgenic egg-laying animal whose somatic and germ line cells contain an expression system comprising (i) a first DNA sequence encoding an immunoglobulin constant region (ii) a second DNA sequence encoding an immunoglobulin variable region and (iii) a regulatory region sufficient to provide for expression of the antibody; and

(b) obtaining an egg from the animal.

28. A method according to claim 27 wherein the constant region is derived from a human gene.